STATEMENT OF WORK
FOR THE CONDUCT OF STUDIES TO EVALUATE
THE POTENTIAL TOXICITY AND CARCINOGENICITY OF CELL PHONE
RADIO FREQUENCY RADIATION IN LABORATORY ANIMALS
FOR THE NATIONAL TOXICOLCOY PROGRAM (NTP)

I. GENERAL PROJECT OBJECTIVES

These studies are designed to characterize the potential toxicity and carcinogenicity of cell phone radio frequency radiation (RFR) in Sprague-Dawley rats and B6C3F1 mice exposed unconstrained in reverberation chambers. More than 100 million Americans use wireless communication devices yet guidelines for cell phone RFR are based largely on protection from acute injury from thermal effects. Little is known about possible health effects of long-term exposure to minimally thermal levels of cell phone RFR.

PROJECT MANAGEMENT

The general study designs for this project are included in this Statement of Work. However, all experimental studies are to be conducted according to Attachment 2, the "Specification for the Conduct of Studies to Evaluate the Toxic and Carcinogenic Potential of Chemical, Biological and Physical Agents in Laboratory Animals for the National Toxicology Program" dated September 2000, with subsequent revisions.

This project will be separated into phases. The BASE contract will consist of Phase 1 and the subsequent Phases 2 through 5 (the thermal pilot study, perinatal/prechronic toxicity study, and chronic study (including the transgenic mice study), respectively) are to be considered Optional.

Phase 1: During phase 1, the contractor shall perform those activities associated with procurement of equipment and materials needed to construct the reverberation chamber exposure and monitoring systems, the construction/renovation of the exposure and monitoring systems, and the developmental effort needed to demonstrate that the systems function appropriately and meet the specifications detailed in Section II. The contractor shall not proceed to subsequent phases until the option for that phase has been exercised.

Option(s) - Phases 2 through 5 (the thermal pilot study, perinatal/prechronic toxicity study, chronic study and transgenic mice study, respectively): Upon successful completion of Phase 1, the Government may unilaterally exercise its options to conduct Phases 2 through 5. Phases 2 through 5 will involve the conduct of studies in which animals will be exposed for up to 110 weeks of age to radio frequency radiation of specified frequencies, power levels, and modulations using the exposure system developed in Phase 1. The Government estimates approximately 16 weeks for the conduct of the Phase 2, thermal pilot study, 56 weeks for the perinatal/prechronic study, and 153 weeks for the chronic study. The optional Phase 5 transgenic mice study shall be conducted simultaneously with the chronic study.

GOVERNMENT FURNISHED MATERIALS: (1) Sprague-Dawley rats and parental strains of the B6C3F1 mouse used in the conduct of these studies; (2) TDMS equipment, software and user manuals; and, (3) Serology testing by an NTP contractor for animal disease screening

NOTE: Offerors are to provide technical responses to all options in their technical proposals so that they can be evaluated and negotiated. As noted in Section L.2., General Instructions, of the RFP, offerors must provide separate direct cost and level of effort information in their TECHNICAL PROPOSAL for the base contract and for each option so that the offeror's understanding of the project may be evaluated.

In the TECHNICAL PROPOSAL SUMMARY OF DIRECT COSTS, labor hours for each Phase must be broken down sufficiently to allow evaluation of the adequacy of effort proposed for each discipline area. For each Phase, labor hours are to be broken down by each individual proposed with name and function identified.

II. PHASE 1- PURCHASE AND DEMONSTRATION OF PROPERLY FUNCTIONING EXPOSURE AND MONITORING SYSTEMS

During Phase 1, the contractor shall:

A. Purchase the needed equipment and materials and construct the reverberation chamber exposure and monitoring systems.

The NTP chronic studies will require a total of 14 reverberation chambers: 3 power levels for mice exposed to 1900 MHz GSM modulated signals, 3 power levels for mice exposed to 1900 MHz CDMA modulated signals, 1 mouse sham chamber, 3 power levels for rats exposed to 900 MHz GSM modulated signals, 3 power levels for rats exposed to 900 MHz CDMA modulated signals, and 1 rat sham chamber.

The size of each chamber is a function of the required uniform field volume, as well as space for paddles and antenna in each chamber, considerations for separation of animals from each other and from all conducting surfaces (walls, floor, ceiling, antennas, and paddles), and space for staff to perform routine animal care and data collection (body weights, body temperature, morbunditity/mortality checks, clinical signs, and change of cages, feed, and water bottles) during non-exposure periods. Exposed animals must be at least 0.5 wavelength from any conducting surface (i.e., 17 cm with 900 MHz radiation and 8 cm with 1900 MHz radiation). The volume of field uniformity can be estimated from the maximum number of animals that shall be individually caged in each chamber. For the chronic studies each chamber shall initially house 200 rats (100 males and 100 females) or 200-240 mice; the larger number of mice reflects the possibility that a transgenic model may also be included. Numerical simulations indicate that absorption deviations due to proximity effects are only about 0.3 dB for rat phantoms (500 ml bottles containing tissue simulating fluid) separated by 0.25 wavelength and exposed to 900 MHz RFR. An absorption deviation of about 0.3 dB was also estimated for mouse phantoms (50 ml bottles) separated by 0.25 wavelength and exposed to 1900 MHz RFR.

An example for estimating the volume of field uniformity is provided here, however, other justified configurations would be acceptable. Cage dimensions for individually housed rats in NTP studies are 10.5”L x 9.5”W x 8”H. A 5-shelf cage rack (with the lowest shelf approximately 1 foot above the floor and 15 inches between shelves) with dimensions 60”W x 15”D x 72”H could hold 25 rat cages (2” spacing between cages). A similar cage rack but with shelves of 24”D could hold 50 rat cages. Thus, 8 single width or 4 double width cage racks shall be needed in each reverberation chamber housing rats during the chronic study. The floor dimension occupied by 8 single-width racks during exposures is approximately 128” x 84” (325 cm x 214 cm), based on 8” (20 cm) separation between racks. Thus, the required volume of field uniformity shall be approximately 450 cubic feet (approximately 13 cubic meters). The required floor area and corresponding volume for the field of uniformity could be reduced by approximately 30% by using double-width cage racks.

Cage dimensions for individually housed mice in NTP studies are 9.25”L x 6”W x 6.12”H. A 5-shelf cage rack (with the lowest shelf approximately 1 foot above the floor and 15 inches between shelves) with dimensions 60”W x 15”D x 72”H could hold 40 mouse cages. A similar cage rack but with shelves of 24”D could hold 80 mouse cages. Thus, 6 single width or 3 double width cage racks will be needed in each reverberation chamber housing mice during the chronic study. The floor dimension occupied by 6 single-width racks during exposures is approximately 108” x 72” (275 cm x 183 cm), based on 4” (10 cm) separation between racks. Thus, the required volume of field uniformity will be approximately 325 cubic feet (approximately 9.3 cubic meters).

Note: All cages, cage covers, cage racks, sipper tubes, and feeders to be purchased after Phase 1 approval shall be composed of non-conductive, low dielectric materials.

Field strength monitoring will be continuous during exposures and measured at two locations within each chamber. Probes must capable of providing a linear response over a 10^4 range. A power meter for each chamber must be capable of monitoring input and received RF power.

Several required features of the reverberation chambers include:

1) chamber and door material must not cause significant loss of electromagnetic energy delivered to each chamber and must be made of a washable, noncorrosive material (e.g., stainless steel); chambers must withstand high pressure water cleaning and sanitation procedures without corrosion or other deterioration
2) the dimensions of the chamber door (>100 cm W x >200 cm H) must be large enough to roll in and out the animal cage racks
3) room shielding must be >100 dB
4) 2 motor controlled stirring paddles will be needed per chamber to create a statistically homogeneous electromagnetic environment; paddle rotations should be adjustable and measurable over the range of 1 to 50 rpm.

Safety features of the chambers shall include:

1) RF power cannot operate with doors open
2) a warning light(s) indicating RF power is on
3) door can be opened from inside
4) automatic power shut down in chamber and emergency warning when the input RF power is out of specification range.

Environmental controls inside chamber shall include:

1) ventilation panels to accommodate air (filtered) exchange of 15 volume changes per hour, which must be continuously recorded
2) temperature control of 75 ± 3^0F, continuously recorded with an alarm system for warning of temperature fluctuations beyond 70-80 degree range
3) humidity control to 40-70%, continuously recorded
4) incandescent lighting (12 hours/day turned on and off by an automatic timer) with RF filtered connections of >90dB
5) noise level control to < 40 dB.

Amplifier requirements and signal generators:

The NTP is pursuing efforts to define GSM and CDMA signal parameters that reflect human exposure conditions and implement these parameters into the rodent health effects studies. Based on dosimetry modeling of specific absorption rates (SAR) distributions in rats and mice exposed to RFR in reverberation chambers (Fröhlich et al., 2003), the NTP has decided that optimum whole body exposures would be achieved with mice exposed to 1900 MHz RFR and rats to 900 MHz RFR. For both species, exposures GSM and CDMA modulated signals shall be used. Until these signals are fully defined, it is not possible to accurately determine the amplifier requirements for these studies. *However, based on several assumptions (which follow) and design features of the chronic study, the offeror shall provide an analysis of amplifier requirements and commensurate costs.*

It is anticipated that in the chronic study, 200 Harlan Sprague-Dawley rats (100 males and 100 females) shall be exposed in reverberation chambers to 900 MHz RFR until survivors reach 110 weeks of age. Separate chambers shall be used for GSM and CDMA modulated signals and for each power level.

Offerors shall assume:

- *the three power levels for each signal during exposure periods will achieve time- average whole body specific absorption rates (SARs) of 6.0, 2.5, and 1.0 W/kg.*
- *exposures will be for 20 hours per day five days per week with continuous cycling of 10 minutes on and 10 minutes off during the exposure periods. By this approach, it will be possible to use the same amplifier to expose each species to GSM and CDMA modulated signals simultaneously (offset only by the 10 minute cycling pattern).*
- *the amplifier requirement will be dominated by the GSM modulated signal with a pulse frequency of 217 Hz and a pulse width of 0.58 msec resulting in a duty cycle of approximately 1/8.*
- *Lastly, that water bottles will contain sufficient water for 2-3 days of consumption and that the absorption efficiency in chambers containing 200 rats is 85%.*

Amplifier requirements and costs shall also be estimated for B6C3F1 mice exposed to GSM and CDMA modulated 1900 MHz signal for up to 110 weeks of age. Offerors shall assume the same average whole body SAR doses as for rats, but assume an absorption efficiency of 50%.

B. Demonstrate that the exposure and monitoring systems function appropriately.

The contractor shall demonstrate that the assembled reverberation chambers meet the specifications listed above concerning room shielding, environmental controls, and implementations of the GSM and CDMA signal parameters (to be defined before the award of the contract). In addition, field uniformity within each empty chamber at 0.5 wavelength from any conducting surface but especially within the specified volume of field uniformity must be demonstrated to be less than ±1 dB (standard deviation), with a maximum variation of less than ±3 dB. SAR measurements with immersible SAR probes placed in water bottles filled with a tissue simulating fluid (phantoms) must also be made to verify the energy transfer function from the uniform field volume in these chambers to a medium of known dielectric properties. The contractor shall validate the methods for the generation and chamber monitoring of RF signals at the protocol required power levels; conduct detailed chamber characterization studies; determine measurement limits, precision, and linearity of the chamber monitoring system.

C. Prepare and submit a Phase 1 Report.

The Phase 1 report shall include:

1) All health and safety activities and procedures related to these RF radiation studies
2) Description of the reverberation chambers
3) Description of the RFR generation and monitoring systems
4) Description of the GSM and CDMA signal generators
5) Data and discussion on the evaluation of field uniformity inside the chamber
6) Standard operating procedure (SOP) for chamber monitoring
7) SOP for field uniformity determinations
8) Room air monitoring methodology, strategy, SOPs, frequency and results

It is estimated that all Phase 1 activities, including submission of the Phase 1 Report shall be completed within 6 months from contract award. NTP review of the Phase 1 Report will be completed within 4 weeks of receipt.

Upon successful completion of Phase 1, the Government may unilaterally exercise its option to authorize work specified as Phase 2. The Contracting Officer will notify the Contractor in writing of the determination to exercise the option to proceed with Phase 2. If no such determination is made, the Task will end at this point. If the option for Phase 2 is exercised, exposure of animals in the thermal pilot study shall begin within 6 weeks of the Contracting Officer's notification of approval to proceed with the Phase 2 option.

III. OPTIONS FOR PHASES 2-5: STUDY PROTOCOLS

A. OPTION - PHASE 2: THERMAL PILOT STUDY PROTOCOL

1. The purpose of the thermal pilot study is to determine the effects of modulated cell phone RFR exposures on body temperature, body weight, and survival of exposed rats and mice. These data will serve as the basis for selecting power levels for the subchronic toxicity study. This study will also include continuous field measurements at two locations in each chamber to monitor field uniformity in the specified volume of field uniformity. Measurements of average SARs during exposures must be made continuously in water bottles (one per chamber) filled with a tissue simulating fluid (phantoms) using immersible field probes or temperature probes with fiber optic cables linked to a remote monitor. Information on the energy transfer function from the uniform field volume in each chamber to a medium of known dielectric properties will be used to verify estimates of animal dosimetry.

2. After a seven-day quarantine period, animals shall be assigned at random (by weight) to treatment and sham control groups. Harlan Sprague-Dawley rats and B6C3F1 mice of different ages (5 and 20 weeks of age) or pregnancy status (~gestation day-10) shall be included in this study. At each of five power levels (time-average whole body specific absorption rates, SARs, of 4, 6, 8, 10, 12 W/kg) plus a sham control group, five animals per species shall be exposed in reverberation chambers to cell phone RFR. Rats shall be exposed to 900 MHz GSM and CDMA modulated signals, and mice to 1900 MHz GSM and CDMA modulated signals. Exposures shall be for 20 hours per day for five days with continuous cycling of 10 minutes on and 10 minutes off during the exposure periods. Because of this continuous cycling pattern, the same amplifier shall be used to concurrently expose each species to the same power level of GSM or CDMA modulated signals (offset only by the 10 minute cycling pattern). An evaluation of the effects of 30-minute on/off cycles on body temperature may also be included on one of the exposure days.

3. The total number of animals required for this study are:

	Group Size, N		Species		Sex		Age		Power levels		Modulation		Total
Exposed	5	x	2	x	2	x	2	x	5	x	2	=	400
Controls	5	x	2	x	2	x	2	x	1			=	40
													440
Pregnant animals													
Exposed	5	x	2	x	1	x	1	x	5	x	2	=	100
Controls	5	x	2	x	1	x	1	x	1			=	10
													110

4. All rats and mice shall be housed individually. Food and water (in bottles) shall be available ad libitum. Separate chambers will be needed for rats and mice at each power level and modulation. Males and females of each species shall be exposed in the same chamber.

5. The feasibility of using subcutaneously implanted programmable temperature microchips (2.2 x 14 mm, weighing 120 mg; see Kort et al. in Lab Animals 32: 260-269, 1998) to monitor body temperature during exposure of rats and mice to RFR in reverberations chambers is undergoing evaluation. If this technology is found to be feasible for the purposes of the thermal pilot study, then it shall be used in these studies. Otherwise, rectal thermistor probes shall be used to measure the effects of RFR exposures on body temperature of rats and mice. Body temperatures shall be

recorded immediately after power is shut off at one hour, 5 hours (during the 10 minute off cycle), and 20 hours of exposure after one, three, and five days of treatment.

6. Animals shall be weighed individually on day one of the study and at the end of the 5-day exposure. Animals shall be observed two times daily, once in the morning and once in the afternoon for moribundity and death. Observations shall be made twice daily for clinical signs of toxicologic effects of the exposure. Clinical signs shall be recorded daily by animal number and made a part of the study report. Water consumption for each animal shall be recorded daily.

7. Animals in this study shall not be examined for gross or microscopic lesions. The left eye shall be removed from each animal and stored under conditions appropriate for evaluations of optical quality of the lens and then shipped to NTP. Shipping instructions shall be provided.

8. Male rats and female mice that began the 5-day exposure (sham and 5 power levels, 2 modulations) at 20 weeks of age (50 exposed rats and 50 exposed mice plus 5 control rats and 5 control mice) shall be processed for examination of brains by magnetic resonance microscopy. After the last exposure, animals shall be saline flushed and perfusion fixed. A protocol will be provided shortly on how brains should be collected, fixed, and shipped to NTP for MRM evaluations.

9. The results of the thermal pilot study shall be reported in the Thermal Pilot Study Report. (See Section IV.I for due date and number of copies required).

It is estimated that the Phase 2 Report shall be completed within 4 weeks after the last animal exposure. NTP review of the Phase 2 Report will be completed within 4 weeks of receipt.

Upon successful completion of Phase 2, the Government may unilaterally exercise its option to authorize work specified in Phase 3. The Contracting Officer will notify the Contractor in writing of the determination to exercise the option to proceed with Phase 3. If no such determination is made, the Task will end at this point. If the option for Phase 3 is exercised, exposure of animals in the perinatal/prechronic study shall begin within 6 weeks of the Contracting Officer's notification of approval to proceed with the Phase 3 option.

B. OPTION - PHASE 3 - PERINATAL/PRECHRONIC TOXICITY STUDY PROTOCOL

1. The purpose of this study is to determine toxic effects of cell phone RFR and to determine appropriate power levels for each strain and species to be used in the chronic toxicity/carcinogenicity study. This study shall include continuous field measurements at two locations in each chamber to monitor field uniformity in the specified volume of field uniformity. Measurements of average SARs during exposures must be made continuously in water bottles (one per chamber) filled with a tissue simulating fluid (phantoms) using immersible field probes or temperature probes with fiber optic cables linked to a remote monitor. Information on the energy transfer function from the uniform field volume in each chamber to a medium of known dielectric properties will be used to verify estimates of animal dosimetry.

2. Male and female Harlan Sprague-Dawley rats and the parental strains of the B6C3F1 mouse (C57BL6 and C3H) shall be approximately 7-8 weeks of age upon receipt. The F_0 rats and mice shall be housed separately for a 10-14 day quarantine period. Then, one breeder male shall be housed with 2 breeder females. During cohabitation, vaginal smears are to be taken daily to determine the presence of sperm. Adequate females are to be bred to produce the required number of pregnant dams within a 1-week period so that F1 rats and mice are approximately the same age (18-25 days) when weaned. Breeder males shall be discarded after breeding. The pregnant dams shall be randomly assigned to treatment and sham control groups and housed individually. At each of four power levels plus a control group, ten pregnant animals per species shall be exposed to cell phone RFR in reverberation chambers beginning on gestation day-6. Programmable temperature microchips (2.2 x 14 mm, weighing 120 mg) shall be subcutaneously implanted into pregnant rats

and mice on gestation day-6. Rats shall be exposed to 900 MHz GSM and CDMA modulated signals, and mice shall be exposed to 1900 MHz GSM and CDMA modulated signals. The exposure schedule shall be five days per week, weekdays only and exclusive of holidays. The exposure times shall be 20 hours per day with continuous cycling of 10 minutes on and 10 minutes off during the exposure periods. The same amplifier shall be used to concurrently expose each species to the same power level of GSM and CDMA modulated signals (offset only by the 10 minute cycling pattern). Time-average whole body SAR levels during gestational and lactational exposures shall be based on dosimetry in the dam; SAR levels during lactation and after weaning shall be based on dosimetry in the offspring. Separate chambers will be needed for rats and mice at each power level and modulation. All animals shall remain on the treatment regimen until the day of sacrifice. All rats and mice shall be housed individually during gestational exposures.

3. The total number of pregnant animals required for the gestational exposures are:

	Group Size, N		Species		Power levels		Modulation		Total
Exposed	10	x	2	x	4	x	2	=	160
Controls	10	x	2	x	1			=	20
									180

4. On postnatal day (PND)-4, rats shall be culled to 8 per litter (4 males and 4 females) and mice to 6 per litter (3 males and 3 females). At weaning (~postnatal day-21), dams will be removed (without further evaluation), pups shall be separated by sex, and litter size shall be reduced to 2 males and 2 females for 4 weeks more of exposure (i.e., until PND-49). Animals selected for continued exposure should be those with body weights near the mean of the litter for that sex. On PND-35, animals shall be individually caged and programmable temperature microchips will be subcutaneously implanted into all rats and mice. Groups of 10 male and 10 female rats and mice from separate litters will be identified for histopathologic evaluations, the other 10 animals per group will be used for determination of blood brain barrier leakage. Food and water (in bottles) shall be available ad libitum. The feasibility of using subcutaneously implanted programmable temperature microchips (2.2 x 14 mm, weighing 120 mg; see Kort et al. in Lab Animals 32: 260-269, 1998) to monitor body temperature during exposure of rats and mice to RFR in reverberations chambers is undergoing evaluation. If this technology is found to be feasible for the purposes of the thermal pilot study, then it will be used in these studies. Otherwise, rectal thermistor probes shall be used to measure the effects of RFR exposures on body temperature of rats and mice. Body temperatures shall be recorded immediately after power is shut off.

5. The total number of rats and mice required for the postlactational exposures are:

	Group Size, N		Species		Sex		Power levels		Modulation		Total
Exposed	20	x	2	x	2	x	4	x	2	=	640
Controls	20	x	2	x	2	x	1			=	80
											720

6. Pregnant animals shall be weighed individually on gestation day-6 and at weekly intervals throughout the gestation and lactation periods. Litters shall be examined for number of live and dead pups at delivery, sex ratios, per cent survival during lactation, and body weights of pups on postnatal days 1, 4, 7, 14 and 21. Pup body weights shall be recorded weekly thereafter and at necropsy on PND-49.

7. Animals shall be observed twice daily throughout the study, once in the morning and once in the afternoon, including holidays and weekends for signs of moribundity or death. Signs of

toxicity noticed during these routine checks shall be recorded. Animals whose condition makes it unlikely that they will survive until the next observation, based on criteria established by the Principal Investigator in concert with the veterinary staff and toxicologist, shall be sacrificed immediately, necropsied, and diagnosed histopathologically. Histopathology shall be performed in accordance with the Histopathology Specifications (Specifications – Section II.H). Formal clinical observations shall be performed and recorded weekly. Water consumption by cage shall be recorded weekly during all phases of the study (gestational day 6 through PND-49).

8. Organ weights shall be determined from all animals surviving until the end of the study (PND-49). Organs to be weighed are: brain, liver, thymus, right kidney, right testis, heart, right adrenal gland, and lungs. Organs shall be weighed to the nearest 10.0 mg except for testis, adrenal gland, and thymus, which shall be weighed to the nearest 1.0 mg. Organ/body weight ratios shall be calculated. See Histopathology Specifications Section II.H for specific tissue trimming instructions.

9. A complete gross necropsy shall be performed on all exposed and sham control animals in the groups exposed from PND-21 to PND-49 that either die early or are sacrificed during and at the end of the study. The left eye shall be removed from each animal and stored under conditions to be described later and then shipped to NTP for evaluations of optical quality of the lens. All tissues as listed in NTP Specifications shall be saved in formalin.

Except for animals specified for determination of blood brain barrier leakage, all tissues required for complete histopathology as listed in the NTP Specifications shall be trimmed, embedded, sectioned and stained with hematoxylin and eosin for possible histopathologic evaluation. Gross lesions shall be examined in all animals in all exposure groups plus controls. A complete histopathologic evaluation shall be done on all control animals, all animals in the highest exposure group with at least 60% survivors at the time of sacrifice, plus all animals in higher exposure groups. Exposure-related lesions (target organs) shall be identified and examined in lower exposure groups to a no-effect level. For all natural death/moribund sacrifice animals a complete histopathologic evaluation shall be performed. Histopathology shall be performed in accordance with the Histopathology specifications indicated in Specifications – Section II.H.

10. Special studies:

a. Core body temperature

Temperature measurements shall be recorded from animals with the implanted programmable temperature microchips (pregnant rats and pups exposed from PND-35 to PND-49) immediately after power is shut off on the following schedule: body temperatures of dams shall be recorded on gestation days 7, 11, and 16 and on postnatal days 1, 4, 7, and 14; body temperatures of pups shall be recorded on postnatal days 36, 40, and 47. If ongoing studies indicate that this technology is not feasible for determining body temperature of animals exposed to RFR in reverberation chambers, then rectal thermistor probes shall be used to measure the effects of RFR exposures on body temperature of rats and mice.

b. Plasma corticosterone

Blood samples shall be collected in the morning immediately following the last exposure (PND-49) for analyses of plasma corticosterone levels in exposed and sham control animals. The contractor shall demonstrate proficiency in collecting and analyzing blood samples for corticosterone levels prior to the study start.

c. Blood brain barrier leakage

Ten animals per group that were exposed to modulated RFR from PND-35 to PND-49 were designated for determination of blood brain barrier leakage. The procedure of Guerin et al. (Neuroscience 103:873-883, 2001) that measures blood vessel permeability to fluorescent dextrans shall be used for these analyses. Following the last exposure, rats and mice shall be given iv injections of a combination of fluorescent dextrans of different molecular weights (10,000 mol. wt. dextran-orange green with 70,000 mol. wt. dextran-rhodamine). One hour following injection of the fluorescent tracer, animals shall be anesthetized and then perfusion fixed with 4% paraformaldehyde. The preparation of sections for viewing with a laser scanning confocal microscope are described by Guerin et al. (2001).

d. Brain evaluations in culled pups

Brains from one male rat and one female mouse culled from each litter at PND-4 and PND-21 shall be collected, fixed, and shipped to NTP for evaluation of altered cell migration patterns. Methods for the collection, fixation and shipping of brains will be provided.

11. Ten serum samples from rats and ten from mice shall be collected for the Animal Disease Screening Program from the sham controls at PND-49. (See Specifications – Section II.D.13)

12. Data from the in-life portion and pathology for the prechronic test shall be entered on TDMS.

13. The results of this study shall be reported in the Perinatal-Prechronic Study Report. (See Section IV.I. for the due date and number of copies required.)

It is estimated that the Phase 3 Report shall be completed within 16 weeks after the terminal necropsy. NTP review of the Phase 3 Report will be completed within 4 weeks of receipt.

Upon successful completion of Phase 3, the Government may unilaterally exercise its option to authorize work specified in Phase 4. The Contracting Officer will notify the Contractor in writing of the determination to exercise the option to proceed with Phase 4. If no such determination is made, the Task will end at this point. If the option for Phase 4 is exercised, exposure of animals in the chronic study shall begin within 6 weeks of the Contracting Officer's notification of approval to proceed with the Phase 4 option.

C. OPTION – PHASE 4: CHRONIC STUDY PROTOCOL

1. This study is designed to determine the chronic toxicity and potential carcinogenicity of cell phone RFR in laboratory animals. This study shall include continuous field measurements at two locations in each chamber to monitor field uniformity in the specified volume of field uniformity. Measurements of average SARs during exposures must be made continuously in water bottles (one per chamber) filled with a tissue simulating fluid (phantoms) using immersible field probes or temperature probes with fiber optic cables linked to a remote monitor. Information on the energy transfer function from the uniform field volume in each chamber to a medium of known dielectric properties will be used to verify estimates of animal dosimetry.

2. Male and female Harlan Sprague-Dawley rats and the parental strains of the B6C3F1 mouse (C57BL6 and C3H) shall be approximately 7-8 weeks of age upon receipt. The F_0 rats and mice shall be housed separately for a 10-14 day quarantine period. Then, one breeder male shall be housed with 2 breeder females. During cohabitation, vaginal smears are to be taken daily to determine the presence of sperm. Adequate females are to be bred to produce the required number

of pregnant dams within a 1-week period so that F1 rats and mice are approximately the same age (18-25 days) when weaned. Breeder males shall be discarded after breeding. The pregnant dams shall be randomly assigned to treatment and sham control groups and housed individually. At each of three power levels (based on results of the prechronic studies) plus a sham control group, 50 pregnant animals per species shall be exposed to cell phone RFR in reverberation chambers beginning on gestation day-6. Rats shall be exposed to 900 MHz GSM and CDMA modulated signals, and mice shall be exposed to 1900 MHz GSM and CDMA modulated signals. The exposure schedule shall be five days per week, weekdays only and exclusive of holidays. The exposure times shall be 20 hours per day with continuous cycling of 10 minutes on and 10 minutes off during the exposure periods. The same amplifier shall be used to concurrently expose each species to the same power level of GSM and CDMA modulated signals (offset only by the 10 minute cycling pattern). Time-averaged whole body SAR levels during gestational exposures shall be based on dosimetry in the dam; SAR levels during lactation and after weaning SAR shall be based on dosimetry in the offspring. Separate chambers will be needed for rats and mice at each power level and modulation. All animals shall remain on the treatment regimen until the day of sacrifice. All rats and mice shall be housed individually during gestational exposure.

3. The total number of pregnant animals required for the gestational exposures are:

	Group Size, N		Species		Power levels		Modulation		Total
Exposed	50	x	2	x	3	x	2	=	600
Controls	50	x	2	x	1			=	100
									700

4. On PND-4, rats shall be culled to 8 per litter (4 males and 4 females) and mice to 6 per litter (3 males and 3 females). At weaning (~postnatal day-21), dams shall be removed (without further evaluation), pups shall be separated by sex, and litter size shall be reduced to 2 males and 2 females (animals selected for continued exposure should be those with body weights near the mean of the litter for that sex) for chronic exposure (until 110 weeks of age, which is similar in age to typical NTP 2-year studies in which animals begin exposure at about 6 weeks of age). On PND-35, all animals shall be individually caged. Food and water (in bottles) shall be available ad libitum; however, because absorption of RFR by water could require increased amplifier power to maintain the targeted SAR levels during the chronic exposure, the water bottles should be limited to approximately 2-3 times the expected 24-hour consumption amounts and checked or adjusted daily.

5. The total number of rats and mice required for the postlactational exposures are:

	Group Size, N		Species		Sex		Power levels		Modulation		Total
Exposed	100	x	2	x	2	x	3	x	2	=	2400
Controls	100	x	2	x	2	x	1			=	400
Sentinels	15	x	2	x	2			x	2	=	120
											2920

6. On PND-35, programmable temperature microchips (2.2 x 14 mm, weighing 120 mg) shall be implanted subcutaneously into groups of 10 rats and 10 mice per sex per dose that shall be specifically designated for temperature measurements and urinalyses. These animals shall be included in the evaluations of chronic effects. The feasibility of using subcutaneously implanted programmable temperature microchips (2.2 x 14 mm, weighing 120 mg; see Kort et al. in Lab Animals 32: 260-269, 1998) to monitor body temperature during exposure of rats and mice to RFR in reverberations chambers is undergoing evaluation. If this technology is found to be feasible for the purposes of the thermal pilot study, then it will be used in these studies.

Otherwise, rectal thermistor probes shall be used to measure the effects of RFR exposures on body temperature of rats and mice. Body temperatures shall be recorded immediately after power is shut off.

7. An interim sacrifice shall be performed when animals are 19 weeks of age (N=10, equivalent to the age of animals at the end of typical NTP 13-week studies). No more than one animal per original litter shall be included in any group designated for interim sacrifice. Thus, the group size for chronic exposures is 90 per sex per species per power level.

8. Pregnant animals shall be weighed individually on gestation day-6 and at weekly intervals throughout the gestation and lactation periods. Litters shall be examined for number of live and dead pups at delivery, sex ratios, percent survival during lactation, and body weights of pups on postnatal days 1, 4, 7, 14, and 21. Pup body weights shall be recorded weekly thereafter until they reach 19 weeks of age, after that time individual body weights shall be recorded at 4-week intervals. If life threatening tumors develop or a significant number of deaths occur in the groups, the weighing frequency may be increased to every two weeks upon approval by the NTP Project Officer. Animals shall be weighed at the time exposure ceases and again at necropsy., TDMS shall be used for each chronic animal group weighing.

9. Animals shall be observed twice daily throughout the study, once in the morning and once in the afternoon, including holidays and weekends for signs of moribundity or death. Animals whose condition makes it unlikely that they will survive until the next observation, based on criteria established by the Principal Investigator in concert with the veterinary staff and toxicologist, shall be sacrificed immediately, and necropsied. Slides may be required to be prepared within 30 days for histopathologic examination when notification is given (See Specifications – Section II.H). The NTP Project Officer shall be notified immediately of perceived potential threats to the health of the colony. Two copies of the IANRs, with gross information for all early death animals, including sacrifices, shall be forwarded to the NTP Project Officer on the first and fifteenth day of each month. The IANR must be signed by the reviewing pathologist and must include the probable cause of death or morbundidity based on gross observations. Detailed clinical observations shall be made at four-week intervals. The Principal Investigator, laboratory animal veterinarian, toxicologist, or pathologist shall visit the animal rooms periodically and examine the animals to confirm, correct, or expand the clinical observations made by the technicians. This shall be done as often as necessary, but at least once every two weeks, preferable once a week.

10. Each animal shall be formally examined for clinical signs of toxicity at four-week intervals and these observations shall be recorded on TDMS. Signs of toxicity detected at times other than the formal four-week observations shall be noted and recorded on TDMS. The Principal Investigator, toxicologist, and/or study director shall review clinical observations frequently to assure that the information is properly recorded as well as used during the study and to see that they are being made consistently from one observation time to another. Clinical observations made on an animal shall not be open ended or have gaps during the course of the study.

11. All animals from all exposure groups and sham control group(s) that die or are sacrificed during and at the end of the chronic exposure shall receive a complete necropsy examination. Any sentinels found dead or moribund during the course of the study shall receive necropsies. All tissues from all animals shall be preserved in formalin as specified in the NTP Specifications (Section II.H). All gross lesions and all organs/tissues required for complete histopathologic examination shall be trimmed, embedded, sectioned and stained with hematoxylin and eosin for histopathologic examination. This shall be done for all animals in the sham control and all treatment groups.

12. All animals that die (or are sacrificed at 19 weeks or because they are in a moribund condition) shall be subjected to a complete necropsy and slides of all tissues required for complete histopathologic evaluation shall be prepared and evaluated. PEIS Individual Animal Necropsy

Records for these animals shall be submitted to the NTP Project Officer on the 1st and 15th day of each month. As a routine, the complete histopathologic evaluation of these tissues shall be conducted at the end of the study. However, if histopathology evaluation on early death/sac animals is requested earlier by the NTP, it shall be completed within 30 days of notification. Animals that survive until the end of the study shall be given a complete necropsy and histopathologic evaluation without allowing for a recovery period. All tissues required for complete histopathology shall be evaluated in all treatment groups and controls. This is true for all exposure groups including sham controls, both sexes and both species.

13. Because the brain is a potential target of RFR, more than 3 sections per animal shall be examined histopathologically in this study. Paraffin blocks shall be made for 12 portions of the brain from each animal in the 2-year study; 6 of these shall be sectioned for histopathologic evaluation. The other 6 portions of brain shall be available for additional histopathology if needed. A protocol will be provided on how to select, collect and section the appropriate samples.

14. Special studies

a. Core body temperature

Temperature measurements shall be recorded weekly from animals with the programmable temperature microchips starting at 5 weeks of age when the chips are implanted and monthly from 19 weeks to 52 weeks of age. Body temperatures must be recorded immediately after power is shut off. If ongoing studies indicate that the microchip technology is not feasible for determining body temperature of animals exposed to RFR in reverberation chambers, then rectal thermistor probes shall be used to measure the effects of RFR exposures on body temperature of rats and mice.

b. Urinalyses

16-hour urine samples shall be collected from groups of 10 male rats from exposure and control groups after 5 consecutive days of exposure in reverberation chambers at 6, 12, 24, and 50 weeks of age. These samples shall be subjected to metabonomic analyses (e.g., HPLC-MS described by Plumb et al., Analyst 128: 819-823, 2003, or ^{1}H-NMR profiling described by Keun et al., Chem. Res. Toxicol. 15: 1380-1386, 2002; other justified approaches will also be considered).

1-2 ml portions of each urine sample shall also be analyzed for 6-hydroxymelatonin sulfate by radioimmunoassay; reported results must be normalized to creatinine concentration (e.g., see Bakos et al., Bioelectromagnetics, 23: 245-248, 2002). The contractor shall demonstrate proficiency in collecting urine and measuring 6-hydroxymelatonin prior to study start.

c. Hematology

Rats and mice (N=10) shall be bled at the 19-week sacrifice for hematologic determinations. These evaluations shall include:

Erythrocyte count
Mean corpuscular volume
Hemoglobin
Packed cell volume
Mean corpuscular hemoglobin
Mean corpuscular hemoglobin concentration
Erythrocyte morphologic assessment
Leukocyte count
Leukocyte differential
Reticulocyte count

Platelet count and morphologic assessment

See Specifications – Section II.G for details regarding the conduct of clinical laboratory studies. The results of all automated measurements for clinical pathology (unaudited data) shall be reported to the NTP within 21 days after sample collection.

d. Organ weights

Individual body weights and the following organ weights shall be recorded at the 19-week necropsy: brain, liver, thymus, right kidney, right testis, heart, right adrenal gland, and lungs. Organs shall be weighed to the nearest 10.0 mg except for testis, adrenal gland, and thymus, which shall be weighed to the nearest 1.0 mg. Organ/body weight ratios shall be calculated. See Histopathology Specifications Section II.H for specific tissue trimming instructions.

e. Micronuclei and DNA strand breaks

Two unstained blood smears shall be prepared from mice (N=10 per group) at the 19-week sacrifice for use by the NTP for micronuclei determinations (See Specifications – Section II.G.3). At the time of necropsy, smears of bone marrow cells collected from both femurs of rats (N=10 per group) shall be prepared for micronuclei determinations (for sample reference on preparation of bone marrow cells see Vijayalaxmi et al., International Journal of Radiation Biology. 77: 1109-1115, 2001). Slides shall also be immunostained for kinetochore proteins to distinguish between acentric micronuclei produced by chromosome breaks and micronuclei containing a centromeric region, likely produced by chromosome loss (for sample reference on staining procedure see Ranaldi et al., Mutatation Research 491: 81-85, 2001).

In addition, brain cells from rats and mice shall also be analyzed for DNA strand breaks by the comet assay/gel electrophoresis method (for sample reference on preparing cell suspensions and comet assay see Malyapa et al. radiation Research149: 637-645, 1998). The contractor shall demonstrate proficiency in evaluating micronuclei and DNA strand breaks prior to study start.

f. Sperm morphology/vaginal cytology evaluation (SMVCE)

SMVCE shall be conducted on rats and mice sacrificed at 19-weeks of age in accordance with the protocol in the Appendix 5 of the NTP Specifications.

15. OPTION – Phase 5 -- Study in transgenic mice

Because brain carcinogenesis is a major concern of exposure to cell phone RFR, studies in a transgenic mouse model may be performed along with the conventional mouse model. A study in transgenic mice will be included, if a well characterized strain is demonstrated to be susceptible to brain tumor induction by exogenous agents. Two models under consideration are the Nf1;Trp53 model that is heterozygous for two tumor-suppressor genes (Reilly et al., Nature Genetics 26: 109-113, 2000) and the K-ras;Akt model that has mutations in two oncogenes (Holland et al., Nature Genetics, 25: 55-57, 2000). Any newer models that meet the above requirement will also be considered for these studies. Exposures of transgenic mice, which are not expected to continue beyond 9 months of age, shall be in the same reverberation chambers housing the B6C3F1 mice. All transgenic mice from all exposure groups and sham control groups shall receive a complete necropsy and histopathological evaluation.

a. The total number of pregnant animals required for the gestational exposures are:

Group	Power	Modulation	Total

	Size, N		levels				
Exposed	20	x	3	x	2	=	120
Controls	20	x	1			=	20
							140

b. On PND-4, mice shall be culled to 6 per litter (3 males and 3 females). At weaning (~postnatal day-21), dams shall be removed (without further evaluation), pups shall be separated by sex, and litter size shall be reduced to 2 males and 2 females (animals selected for continued exposure should be those with body weights near the mean of the litter for that sex). On PND-35, all animals shall be individually caged. Food and water (in bottles) shall be available ad libitum; however, because absorption of RFR by water could require increased amplifier power to maintain the targeted SAR levels during the chronic exposure, the water bottles should be limited to approximately 2-3 times the expected 24-hour consumption amounts and checked or adjusted daily.

c. The total number of mice required for the postlactational exposures are:

	Group Size, N		Sex		Power levels		Modulation		Total
Exposed	40	x	2	x	3	x	2	=	480
Controls	40	x	2	x	1			=	80
									560

d. Pregnant animals shall be weighed individually on gestation day-6 and at weekly intervals throughout the gestation and lactation periods. Litters shall be examined for number of live and dead pups at delivery, sex ratios, percent survival during lactation, and body weights of pups on postnatal days 1, 4, 7, 14, and 21. Pup body weights shall be recorded weekly thereafter. Animals shall be weighed at the time exposure ceases and again at necropsy., TDMS shall be used for each chronic animal group weighing.

e. Animals shall be observed twice daily throughout the study, once in the morning and once in the afternoon, including holidays and weekends for signs of moribundity or death. Animals whose condition makes it unlikely that they will survive until the next observation, based on criteria established by the Principal Investigator in concert with the veterinary staff and toxicologist, shall be sacrificed immediately, and necropsied. Slides may be required to be prepared within 30 days for histopathologic examination when notification is given (See Specifications – Section II.H). The NTP Project Officer shall be notified immediately of perceived potential threats to the health of the colony. Two copies of the IANRs, with gross information for all early death animals, including sacrifices, shall be forwarded to the NTP Project Officer on the first and fifteenth day of each month. The IANR must be signed by the reviewing pathologist and must include the probable cause of death or morbundidity based on gross observations. Detailed clinical observations shall be made at four week intervals. The Principal Investigator, laboratory animal veterinarian, toxicologist, or pathologist shall visit the animal rooms periodically and examine the animals to confirm, correct, or expand the clinical observations made by the technicians. This shall be done as often as necessary, but at least once every two weeks, preferable once a week.

f. Each animal shall be formally examined for clinical signs of toxicity at four-week intervals and these observations shall be recorded on TDMS. Signs of toxicity detected at times other than the formal four-week observations shall be noted and recorded on TDMS. The Principal Investigator, toxicologist, and/or study director shall review clinical observations frequently to assure that the information is properly recorded as well as used during the study and to see that they are being

made consistently from one observation time to another. Clinical observations made on an animal shall not be open ended or have gaps during the course of the study.

g. All animals from all exposure groups and sham control group(s) that die or are sacrificed during and at the end of the chronic exposure shall receive a complete necropsy examination. All tissues from all animals shall be preserved in formalin as specified in the NTP Specifications (Section II.H). All gross lesions and all organs/tissues required for complete histopathologic examination shall be trimmed, embedded, sectioned and stained with hematoxylin and eosin for histopathologic examination. This shall be done for all animals in the sham control and all treatment groups.

IV. MILESTONE SCHEDULE AND DELIVERABLES

Narrative reports shall include charts, graphs, tabulations and pictures as necessary for explanation or support of the narrative. All final reports shall be dated and signed by the individual(s) responsible and the QAU. Reporting requirements are listed in the table at the end of this section. Also listed in the tables are the due dates and number of copies required. All reports shall be sent directly to the appropriate recipient as indicated in the table. The NTP will supply names of individual recipients as indicated.

A. PERIODIC REPORTS

1. Monthly Progress Report

A Monthly Progress Report shall be mailed by the fifteenth day of each month. Each Monthly Progress Report shall be submitted in the format specified in Specifications, Section III.C.1. No QAU audit of this progress report is required.

2. Sanitization Methods Report

A Sanitization Methods Report shall be due 90 days after contract award and shall describe in detail:

a. The methods being used (and/or proposed for future use) for sanitization of equipment used in the studies to include at least cages, racks, feeders, water bottles, reverberation chambers, electromagnetic field generating system, rooms, walls, halls and buildings. Describe methods in detail, including commercial products used, their EPA registration number and their chemical constituents if possible. Include any change made in procedure or products used in the appropriate Monthly Progress Report.

b. The methods in use to keep animal quarters free of insects and other vermin. Again, specify commercial products used, EPA registration number and their chemical constituents, if possible. Report any changes in procedures or products used in the appropriate Monthly Progress Report.

3. Water Analysis

Water samples shall be collected for analysis and a report of the results submitted to the NTP at least once per year. An analysis is required during the in-life portion of the prechronic study and once each year during the chronic study. For laboratories that are not currently conducting studies for NTP, a report shall also be submitted within 30 days of contract award.

4. Health and Safety Chemical Hygiene Plan (General Facility Plan)

An NTP approved Health and Safety Plan is required prior to any work commencing under the contract. An updated Health and Safety plan shall be submitted to the NTP for review and approval every two years and anytime it is modified. Action to correct deficiencies shall be taken within 30 days of notification that such action is required.

B. PHASE 1 REPORT

This report shall describe the RF generation and exposure system and document that exposures meet all requirements of the SOW particularly with respect to frequency, GSM and CDMA signal parameters, field uniformity, and available power. This report (see page 4 and Table H below) will be reviewed and approval by NTP must be granted prior to the start of animal studies.

C. STUDY REPORTS

1. Thermal Pilot Study Report. This report shall be submitted in accordance with instructions in the table in Section H below.
2. Perinatal/Prechronic Study report. These reports shall be submitted in accordance with the prechronic format instructions in Specifications, Section III.C.2. and the table in Section H below.

3. Chronic Study Reports. These reports shall be submitted in accordance with the instructions in Specifications, Section III.C.3. and the table in Section H below. The report shall be dated and signed by the individual(s) responsible and the QAU Auditor. The transgenic mouse study shall be reported at the same time as the chronic study as a separate chapter in the chronic study report.

D. SUBMISSION OF ARCHIVAL MATERIALS

1. Archival Materials (Study Data) - See Specifications - Section III.B. for details.
2. Histopathology Materials - See Specifications - Section II.H.9. for details.

E. OTHER REPORTS OR SUBMISSIONS

Other reports/submissions of data are listed in Milestones and Deliverables (Section H below.)

Any incident or unforseeable occurrences not listed in this document, or any physical modifications to the laboratory facilities, as well as any changes in personnel that might have an impact on the conduct and results of the studies shall be reported immediately to the NTP.

F. DELIVERY TERMS

All deliverables required by this Statement of Work shall be delivered f.o.b. destination in accordance with the specifications and by the dates specified herein.

G. PUBLICATION OF RESEARCH RESULTS

It is anticipated that the results of research conducted under the Contract shall be published in the peer reviewed scientific literature. Specific details concerning authorship and technical issues surrounding the publication of the research shall be discussed and agreed upon by the Principal Investigator and the NIEHS Project Officer.

Because premature release of information developed under the contract could be harmful to the public, the Contractor and the Government agree that it is important to consider issues related to the timing of the release of research results when submitting information for publication. With regard to public disclosures of the research to be carried out pursuant to this contract, the Contractor agrees to submit all proposed articles to the Project Officer at least thirty (30) days in advance of submission for publication. Within this thirty day period the Contracting Officer shall inform the Contractor if there are serious concerns raised by the timing of said publication.

Upon receipt of a notification that the Government objects to the publication of said information, the Contractor agrees to withhold submission of said publication for an additional thirty (30) days while the author and the Project Officer discuss the issues raised by the Contracting Officer's notification. The Contractor agrees to give good faith consideration to all such issues and further agrees that it will not knowingly submit for publication any article, abstract or other item which would be harmful to the public welfare; however, the final decision on whether to submit an article for publication shall rest with the author of said publication after the procedures set forth above are followed. Similar procedures shall apply for scientific presentations and meeting abstracts.

H. MILESTONES AND DELIVERABLES

Abbreviation and General Delivery Addresses follow the list of milestones and deliverables.
Exact Names and Addresses to be supplied by the Project Officer.

PERIODIC SUBMISSIONS PER FACILITY	FREQUENCY	DUE DATES	DISTRIBUTION (Number of copies)
Monthly Progress Report	1/Month	Mail by 15th each month	CC (2) CO - Cover Page only
Sanitation Methods	1 only	90 Days after Contract Award	CC (2)
Water Analysis	At a minimum, 1 per year; 1 per prechronic study; 1 per year for chronic studies; for new labs, an analysis is required 30 days after receipt of a new award		CC (2)
Health and Safety Plan		As modified or at least every two years	CC (2)
Health and Safety Data to NTP	1/Year	October 1 each year	HS -- One microfiche copy

PRESTART ACTIVITIES	FREQUENCY	DUE DATES	DISTRIBUTION (Number of copies)
Submission of Phase 1 Report	1	within 6 mos of award	CC (3), CO (Cover page only)
NTP Review and Approval to Proceed to Next Phase	NA	Within 4 weeks of receipt of report	
Study Protocol (with indication of contractor's IACUC approval)	1/species	Prior to study start, within 4 weeks of approval to proceed	CC (2)

THERMAL PILOT STUDY	FREQUENCY	DUE DATES	DISTRIBUTION (Number of copies)
Start of Study	NA	2 weeks from approval of study protocol	
Study Report	1/Species	6 weeks from last exposure	CC (6), CO (Cover page only)
Approval to Proceed to Next Phase	NA	Within 4 weeks of receipt of Thermal Pilot Study report	

PERINATAL/PRECHRONIC TOXICITY STUDY	FREQUENCY	DUE DATES	DISTRIBUTION (Number of copies)
Prestart Report (If lower powers are used than in the thermal pilot study)	1	4 weeks from approval to proceed	CC (3)
Review of Prestart Report to approval to proceed	NA	2 weeks from receipt of report	
Start of Perinatal/prechronic Study	NA	4 weeks from approval to proceed	
Serum Samples for Disease Screening	1/Species	As collected	SA - Send Samples for Evaluation
Prechronic Study Report	1/Species	***Within*** 16 weeks from last day of necropsy;	CC (6), CO (Cover page only)
Slides and Inventory	1/Species	Same as Prechronic Study Report	REP CC, PC - Copy of Transmittal Letter
IANR Forms, Histology Processing Records, and Notification of Storage on TDMS	1/Species	30 days after submission of Prechronic Study Reports	REP CC, PC - Copy of Transmittal Letter to include notification of pathology storage on TDMS
Wet Tissues and Blocks	1/Species	Same as IANRs, etc.	REP CC, PC - Copy of Transmittal Letter
Study Raw Data Archival Records for Prechronic Study and Microfiche	1/Species	Same as IANRs, etc.	REP CC - Copy of Transmittal Letter and Inventory
NTP Review of Data and Decision about Chronic Study	NA	1 month from receipt of Study Reports	

CHRONIC STUDY	FREQUENCY	DUE DATES	DISTRIBUTION (Number of Copies)
Prestart Report (If lower powers used in chronic study)	1	4 weeks from approval to proceed	CC (3)
Review of Prestart Report to approval to proceed	NA	2 weeks from receipt of report	
Chronic Study Start	NA	4 weeks from approval to proceed	
Serum samples for Disease Screening	See II.D.13. of SPECS	As collected	SA - Send Samples for Evaluation
Blood smears from mice for micronuclei determination	1	2 weeks from necropsy	MN - Slides and decoding information MI - Copy of transmittal letter and decoding
Slides for Sperm Morphology/ Vaginal Cytology	Per protocol	As collected	SMVC - Send slides for evaluation CC - Copy of transmittal letter
B6C3F1 Samples for Genetic Monitoring	1	Within one week of collection	GEN
Copies of IANR Forms for Early Deaths	Twice a month	On the 1st and the 15th of each month	CC (2 copies)
Chronic Study Report (to include transgenic mice study)	1/Species	30 weeks after the last sacrifice	CC (6), CO (1Cover page only
IANR Forms, Histology Processing Records, Slides, Blocks and Inventory: Notification of Storage on TDMS	1/Species	Same as above	REP CC, PC, QA - Copy of Transmittal Letter to include notification of pathology storage on TDMS
Wet Tissues And Inventory	1/Species	All materials to be received at Archives **within** 4 weeks after submission of report	REP CC, PC, QA - Copy of Transmittal Letter
Archival Records of Study Raw Data and Microfiche	1/Species	Same as above	REP CC - Copy of Transmittal Letter and Inventory QA - Copy of Transmittal Letter
Contract Expiration	NA	60 days from submission of Study Data/Materials to Archives	

IANR = Individual Animal Necropsy Record
TDMS = Toxicology Data Management System

Abbreviations and General Addresses for Deliverables.
Exact names and addresses to be provided (TBP) by the Project Officer.

The number of copies and recipient are subject to change and will be affected by contract modification.

CC Contracts Coordinator
Research Triangle Park, NC 27709

CO Contracting Office
NIEHS, DERT, RCB
Research Triangle Park, NC 27709

GEN Samples for Genetic Monitoring of Mice
TBP

HS NTP Health and Safety
NIEHS
Research Triangle Park, NC 27709

MI Micronuclei Decoding Information
NIEHS
Research Triangle Park, NC 27709

MN Micronuclei Evaluation
TBP

PC Pathology Coordinator
Research Triangle Park, NC 27709

QA Quality Assurance
NIEHS, NTP, ETP
Research Triangle Park, NC 27709

REP Repositories:
Archival Material - Raw Data
OR
Wet Tissues and Blocks
Durham, NC 27713

SA Sentinel Animal Serum Samples
TBP

SMVC Sperm Morphology/Vaginal Cytology Evaluation
TBP

I. TRACKING SCHEDULES

For the purpose of tracking progress during a test, the contractor shall utilize Status Reports containing milestones for the studies under this contract, including all special studies (i.e., hematology, micronuclei, urinalyses, etc.). Progress with reference to this Status Report shall be reported to the Project Officer and adjustments made as required by the Project Officer monthly.

Instructions for the Completion of the NTP Status Report.

A Status Report will be maintained for this study. On this report, there are three columns of dates, which can accommodate up to three species. For these studies, 2 columns will be used, column 1 for Sprague-Dawley rats and column 2 for B6C3F1 mice. After contract award, estimated (E) dates for each study will be entered onto the study-specific Status Report by the Project Officer with input by the Principal Investigator. If the completion of any event is delayed, a new estimated date of completion is established in consultation with the Project Officer and a new date is entered on the Status Report. Upon completion of an event, the actual date will be entered followed by an "A".

Any change affecting the final due date of a prechronic or chronic report must be approved by the NTP Contracting Officer.

All dates will be entered month, day, year (MM/DD/YY). Changes for each Status Report will be submitted monthly by the Project Officer or Pathology Coordinator for NTP system-wide updating.

Each date ame, i.e., each event in the Status Report, has been included because it is either a deliverable or it needs to be tracked by the Project Officer to accurately follow the progress of the study. Date names are abbreviated on the Status Report. Definitions for them will be provided to the testing laboratories. The events tracked have definite time frames and correspond to the "Milestones and Deliverables" in Section VII.H. above.

Any questions regarding completion of the NTP Status Report will be directed to the NTP Project Officer.